American Journal of Hematology 59:295–301 (1998)

Mantle Cell Lymphoma in the Chinese: Clinicopathological Features and Treatment Outcome

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We report the clinical, molecular, and immunohistological findings of 20 Chinese patients with mantle cell lymphoma diagnosed over a 10-year period. The disease affected mainly elderly patients (median age, 65.5 years) with a male predominance (M/F, 3/1). Eighty percent presented with advanced stage III/IV disease but only 25% had B symptoms. Eighty-five percent had extranodal disease at presentation. Complete remission (CR) and partial remission (PR) were achieved in 45% and 40% of the patients, respectively. There was no difference in the CR rate for patients treated with anthracycline-containing or nonanthracycline-containing regimens (43% and 50%, *P* = 0.67). Disease progression or relapse was observed after a median of 26 months in patients who initially responded to treatment. Extranodal relapse occurred in the central nervous system (n = 1), bone marrow (n = 1), pleura (n = 2), orbit (n = 2), and the gastrointestinal tract (n = 3). The median overall survival (OS) was 52 months but there were no long-term survivors. This was not different from the median OS of 53 months of patients with diffuse large cell (DLC) lymphoma treated in the same center over the same period (log rank, *P* = 0.76). Of the 12 patients who were tested for *bcl*-1 rearrangement by polymerase chain reaction (PCR), five (42%) were positive for rearrangement in the major translocation cluster (MTC) region. The median OS rates were 45 months and 63 months for PCR positive and negative patients, respectively (*P* = 0.97). In conclusion, MCL is a disease mainly of the elderly in the Chinese with a male predominance and most had advanced-stage disease and extranodal involvement at presentation. Clinicopathologic features and treatment outcome were similar to Caucasian patients, in that the disease combined the aggressive nature of DLC lymphoma and the incurability of low-grade lymphoma. Am. J. Hematol. 59:295–301, 1998.

Key words: mantle cell lymphoma; immunophenotype; PCR; survival

INTRODUCTION

Mantle cell lymphoma (MCL) has been recognized recently as a distinct clinicopathologic entity. In the mid 1960s, Lennert et al. [1] recognized a group of non-Hodgkin's lymphoma (NHL) comprising predominantly small cells with irregular and cleaved nuclei, and absence of intermingling blast cells. It was included in the Kiel Classification as ''centrocytic lymphoma'' in the early 1970s [1]. The International Working Formulation, however, did not recognize it as a distinct entity and patients with the disease have been mainly included in the diffuse small cleaved or the follicular small cleaved cell categories. The disease has been widely known as intermediate differentiated lymphocytic lymphoma in the United States, and in the early 1980s, Weisenburger et al. [2] described a follicular variant in addition to the usual diffuse form and called it ''mantle zone variant.'' This histologic variant was shown to have a prognostic impact on the treatment outcome. The consistent demonstration of the t(11;14)/*bcl*-1 rearrangement and similar morphologic and immunophenotypic features in the mantle zone, centrocytic and intermediate differentiated lymphomas led to a consensus that they represented the same entity of MCL [3]. Histologically, MCL is characterized by the neoplastic expansion in the mantle zone by a homogeneous population of small- to medium-sized lymphoid

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Received for publication 22 May 1998; Accepted 12 August 1998

cells with slightly irregular nuclear outline and scanty cytoplasm, resulting in a diffuse and/or nodular pattern. The neoplastic cell population has a specific constellation of surface markers including pan-B antigens with surface immunoglobulin (Ig)M and IgD together with one pan-T antigen CD5. However, they are negative for CD10 and CD23, which help to distinguish this disease from follicular small cleaved cell lymphoma and small lymphocytic lymphoma, respectively. The majority of the cases harbor a specific chromosomal translocation t(11;14)(q13;q32) [4] that places the putative cellular oncogene *bcl*-1 on 11q13 under the enhancer control of the IG heavy chain gene at 14q32. This genetic abnormality is detectable by Southern blot [5,6], polymerase chain reaction (PCR) [7,8] and recently, by fluorescent in situ hybridization [9]. Overexpression of cyclin D1 at the mRNA level [10] and the protein level [11,12] can also be detected on paraffin sections by in situ hybridization and immunohistochemistry. Clinical studies showed that MCL mainly affects the elderly with a male predominance, presenting with advanced disease with marrow, hepatic, and splenic involvement [13–20]. Involvement of extranodal sites such as the gastrointestinal tract and Waldeyer's ring is particularly common. Survival studies in general suggest that MCL is an aggressive disease and is rarely curable by conventional chemotherapy. High IPI (International Prognostic Index) risk score [14,15], frequent mitosis [20], and the blastoid variant [17,21] have been described in some studies as poor prognostic factors. In the literature, there is no data on the clinical features and treatment outcome in Chinese patients with MCL. Here we report our experience of MCL in Chinese patients over a 10-year period.

PATIENTS AND METHODS

Our center is a tertiary referral center for patients with hematological malignancies in Hong Kong, catering to a population of about two million. We see about 100 new patients with lymphoma per year and 99% of patients are Chinese permanent residents of Hong Kong.

Pathology specimens from 42 Chinese patients coded as centrocytic lymphoma, diffuse centroblastic-centrocytic lymphoma, small lymphocytic lymphoma, and low-grade B-cell lymphoma unclassified according to the Kiel classification from 1986–1996 were reviewed. Diagnosis of MCL was confirmed in 20 patients by morphologic criteria. The medical records were retrospectively reviewed and histories, clinical findings, treatment modalities, and follow-up information were collected. All of our cases were reviewed by one hematopathologist (ACL Chan). Patients were staged according to the Ann Arbor system. Staging procedures included computerized tomography of the thorax and abdomen, and bilateral bone marrow biopsies. Immunophenotyping was performed on cryostat sections (14 cases) and paraffin sections (six cases) with standard immunoperoxidase technique. The panel of antibodies used included CD3 (Leu4, Becton Dickinson, San Jose, CA), CD3 (polyclonal, Dako, Glostrup, Denmark), CD5 (Dako), CD10 (J5, Coulter, Hialeah, FL), CD19 (Leu 12, Becton Dickinson), CD20 (L26, Dako), CD22 (Dako), and CD23 (Dako).

Treatment was heterogenous because of variations in age, stage, and symptoms (Table I). All of the patients received some form of chemotherapy. These included chlorambucil alone in five cases, CVP in three cases, COPP in six cases, and anthracycline-containing regimens (CHOP in one, m-BACOD in five).

Detection of t(11;14) by PCR

Twelve cases with retrievable material were tested for t(11;14) by a seminested PCR. Genomic DNA was extracted from 20 16-μm thick snap frozen tissue sections by standard method [22]. First round PCR was performed with a consensus J_H primer 5′-ACC TGA GGA GAC GGT GAC-3′ [23] and an MCL (MCL1) primer 5′-GAT GGG CTT CTC TCA CCT ACT A-3′ [24]. Second round PCR was performed with the same J_H primer and another MCL (MCL2) primer 5′-TCA GGC CCT GAT AGC TCG-3′ [24]. The PCR reaction contained 10 mM Tris-HCl-pH 9.0, 50 mM KCl, 0.1% Triton X-100, 1.5 mM MgCl, 0.2 mM dNTP, 0.5 μM of each primer, and 0.5 U of Taq polymerase. The PCR reaction was heated at 94°C for 2 min and followed by 30 cycles of PCR reaction (94°C for 30 sec, 55°C for 45 sec, and 72°C for 1 min). The reaction was further incubated at 72°C for an additional 10 min at the end of PCR. The PCR products were then fractionated in 2% agarose gel and visualized under UV light after ethidium bromide staining. The specificity of the band was confirmed by Southern hybridization with a radiolabeled 5′-CGG TTA GAC TGT GAT TAG C-3′ oligonucleotide *bcl*-1 probe [7]. The same DNA sample was also subjected to seminested PCR for the t(14;18) translocation. The first set of primers were consensus J_H and 5′-TTA GAG AGT TGC TTT ACG TG-3′ (MBR) [25] and the second set of primers were consensus J_H and 5′-CCA AGT CAT GTG CAT TTC CAC GTC-3′ (MBR) [26]. Nucleic acid integrity for PCR was confirmed by PCR amplification of beta-globin gene with the following set of primers: 5′-GAA GAG CCA AGG ACA GGT AC-3′ and 5′-CAA CTT CAT CCA CGT TCA CC-3′ [27].

Response and Survival Analysis

Response was evaluated after completion of six courses of combination chemotherapy or after six months in patients receiving single-agent therapy. Patients had restaging procedures and all initial involved sites were reassessed. Complete remission (CR) was defined as the

TABLE I. Chemotherapy Regimens

Regimen	Dose and route	Day	Frequency
CHOP			
C, cyclophosphamide	750 mg/m^2 i.v.	1	Repeat every 21 days
H, doxorubicin (Adriamycin)	50 mg/m^2 i.v.	1	
O, vincristine (Oncovin)	1.4 mg/m^2 i.v. (max 2.0 mg)	1	
P, prednisone	100 mg p.o.	1–5	
m-BACOD			
m, methotrexate (+leucovorin)	200 mg/m^2 i.v. (over 15 mins)	8, 15	Repeat every 21 days
B, bleomycin	4 U/m^2 i.v.	1	
A, doxorubicin (Adriamycin)	45 mg/m^2 i.v.	1	
C, cyclophosphamide	600 mg/m^2 i.v.	1	
O, vincristine (Oncovin)	1.4 mg/m^2 i.v.	1	
D, dexamethasone (Decadron)	6 mg/m^2 p.o.	1–5	
CVP			
C, cyclophosphamide	400 mg/m^2/day p.o.	1–5	
V, vincristine	1.4 mg/m^2 i.v.	1	
P, prednisolone	100 mg/m^2/day	1–5	
COPP			
C, cyclphosphamide	650 mg/m^2 i.v.	1, 8	Repeat every 28 days
O, vincristine (Oncovin)	1.4 mg/m^2 i.v.	1, 8	
P, procarbazine	100 mg/m^2 p.o.	1–14	
P, prednisone	49 mg/m^2 p.o.	1–14	
IMVP-16			
Ifosfamide	1 gm/m^2	1–5	
Methotrexate	300 mg/m^2 i.m.	3, 10	
VP-16	100 mg/m^2	1–3	
DHAP			
Cisplatin	100 mg/m^2	1	
Ara-C	2 mg/m^2 i.v. B.d.	1–2	
Dexamethasone	40 mg i.v.	1–4	

disappearance of all symptoms and signs of disease, with complete resolution of all previously abnormal investigations. Partial remission (PR) was defined as a regression of the tumor by more than 50% and no detectable new lesions. Overall survival (OS) was calculated from the date of diagnosis to date of last follow-up or death. Progression-free survival (PFS) was calculated from diagnosis to the date of first reported relapse or progression. The OS of 334 patients with diffuse large cell (DLC) lymphoma treated during the same period in our hospital was analysed and compared with that of MCL. The OS of patients with positive PCR was compared with the PCR-negative patients. Survival curves were plotted by the Kaplan-Meier method and compared by the log-rank test. X^2 or the Fisher's exact test were used to test association in two-way tables. All *P* values referred to are two-sided.

RESULTS

All cases were diagnosed by morphology and expressed pan-B markers CD19, CD20, and CD22. For the 14 cases in which immunophenotyping was performed on cryostat sections, all showed a typical MCL phenotype: CD5+CD10−CD23−. By PCR, t(11;14) could be detected in five of the 12 tested cases (42%) (Fig. 1A,B), and all cases were negative for the characteristic translocation of follicular lymphoma, t(14;18). None of our cases belong to the blastic variant.

The clinical characteristics of patients at presentation are shown in Table II.

Response to Therapy

Nine of 20 (45%) patients achieved CR after initial chemotherapy, eight (40%) had PR, and three (15%) were refractory to primary therapy. The three NR patients attained PR after salvage chemotherapy. Of the CR patients, three each received chlorambucil alone, CVP, and m-BACOD, respectively. Of the nine CR patients, seven relapsed at 1–75 months (median, 26 months) after CR. The sites of relapse included peripheral lymphadenopathy (n = 6), orbit (n = 2), bone marrow (n = 1), Waldeyer's ring (n = 1), esophagus, colon and rectum (one each), pleura (n = 2), and central nervous system (n = 1). They were reinduced with various chemotherapy regimens including IMVP, DHAP, and COPP, respectively and five of the seven died of progressive disease 9–64 months (median, 32 months) after relapse. The other two relapsed patients were alive with disease. One patient attained a CR but died of reactivation of hepatitis B one month after CR. Of the eight PR patients, all received further chemotherapy and had stable disease for

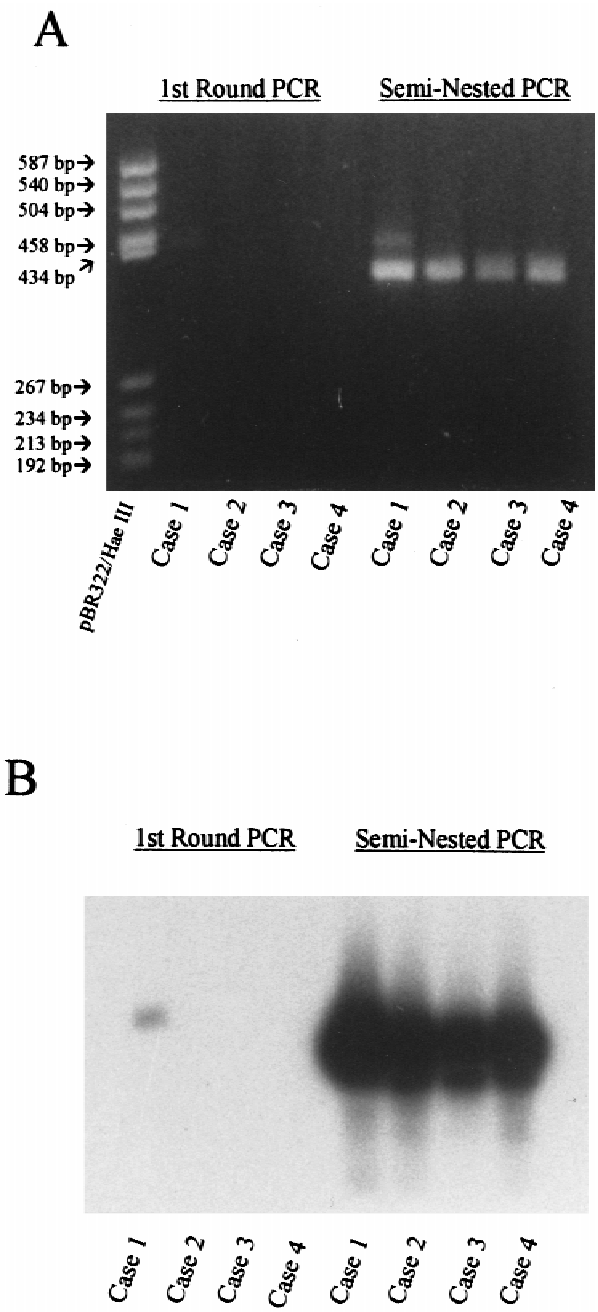

Fig. 1. A: Ethidium bromide staining of seminested PCR product of four t(11;14) positive cases fractionated on and 2% agarose gel and visualized under UV light. B: Specificity of the PCR products by Southern hybridization is confirmed with Southern hybridization with a radiolabeled oligonucleotide *bcl*-1 probe internal to the PCR primers [7].

variable periods (2–54 months; median, 26.5 months) before progression and four died 7–17 months (median, 12.5 months) after disease progression. The three NR patients attained PR after salvage chemotherapy but all died of progressive disease 9–62 months (median, 16 months) from diagnosis. The complete response rates of patients treated with anthracycline-containing and nonanthracycline-containing regimens were 43% and 50% ($P = 0.67$). The median overall survival was 52 months. The projected five-year overall survival is 46% but there were no long-term survivors. The median PFS was 26 months (Fig. 2). The median OS of patients with DLC lymphoma in the same study period was 51 months and the projected 10-year overall survival was 42% at 10 years. There was no statistically significant difference in the OS between DLC and MCL patients (log-rank, $P = 0.76$) (Fig. 3). The median OS rates were 45 months and 63 months for PCR positive and negative cases ($P = 0.97$).

TABLE II. Clinical Features at Diagnosis

Characteristic	No. of patients (%)
n	20
Age at presentation	
<60	6 (30%)
>60	14 (70%)
Sex	
Male	15 (75%)
Female	5 (25%)
Primary site of disease	
Lymph node	14 (70%)
Extranodal sites	17 (85%)
Waldeyer's ring	1 (5%)
Stomach	1 (5%)
Small bowel	2 (10%)
Liver	5 (25%)
Spleen	5 (25%)
Bone marrow	9 (45%)
Ann Arbor stage	
I	0 (0%)
II	4 (20%)
III	2 (10%)
IV	14 (70%)
B symptoms	5 (25%)
LDH level	
Raised	15 (75%)
Normal	5 (25%)
No. of extranodal sites	
None	3 (15%)
One	14 (70%)
Two	3 (15%)

DISCUSSION

Our study showed that MCL in Chinese shared similar clinical features with Caucasian patients. Our study confirmed the elderly majority, male predominance, advanced stage at diagnosis, and the high incidence of extranodal involvement [13–20].

Extranodal involvement at presentation has been found to be common in MCL and occurs in up to 76% of patients [15,20]. In our study, 20% of patents presented with disease in the gastrointestinal tract including Waldeyer's ring, similar to 14–20% reported in other studies [15,17,18,20]. Our study also showed that extranodal

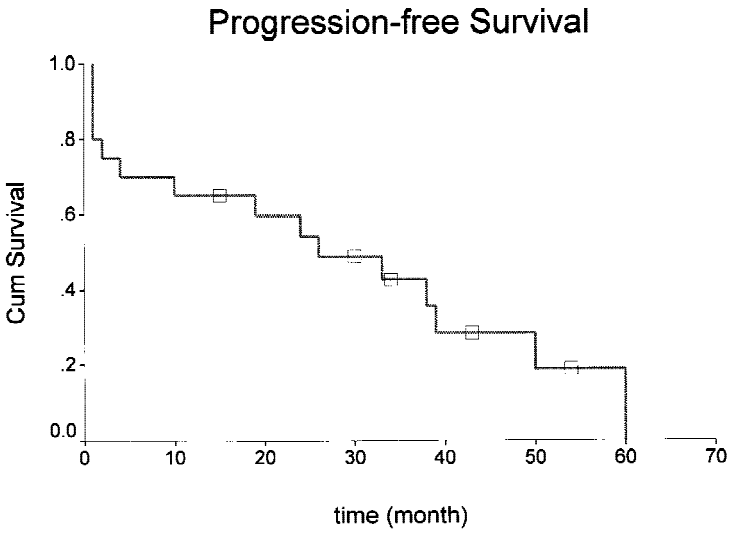

Fig. 2. Progression-free survival (PFS) of patients with mantle cell lymphoma.

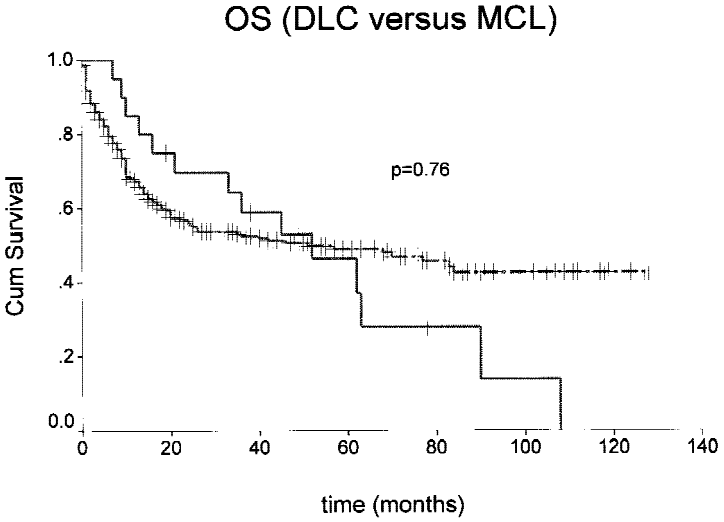

Fig. 3. Overall survival (OS) of patients with diffuse large cell lymphoma (dotted line) and mantle cell lymphoma (solid line).

sites were also frequently involved at relapses, with one case each in the bone marrow and central nervous system, two cases each in the orbit and pleura, and three cases in the gastrointestinal tract.

In contrast to DLC lymphoma where B symptoms are common with advanced-stage disease, various studies showed that B symptoms occurred in less than 50% of MCL patients with stage III/IV disease [13,15,18–20]. In our study, although 80% of patients had advanced stage disease at presentation, only 25% had B symptoms.

Treatment Outcome and the Role of Anthracycline

In this study, the CR rate was 45%, similar to other studies in which the CR rates ranged from 9% to 58% [13,15–20,28].

Although anthracycline is important in the treatment of patients with intermediate- and high-grade non-Hodgkin's lymphoma and induces CR in 50–70% of patients with aggressive lymphoma, its role in MCL is controversial. Most of the current data suggest that addition of anthracycline does not improve the remission rate and the OS [13,14,16,19,20] except one study [15]. Moreover, in a prospective study in which 63 patients with centrocytic lymphoma were randomized to receive either COP (cyclophosphamide, vincristine, and prednisone) or CHOP therapy, no statistically significant differences in CR rates, overall response rate, relapse-free, or overall survival were demonstrated. In keeping with these data, our study showed that there was no difference in the response rate of patients receiving anthracycline-containing regimens and non-anthracycline containing regimens (43% vs. 50%, $P = 0.61$). In fact, there is evidence that [16] different regimens do not influence the natural course of the disease.

The median OS in our patients was 52 months. This is at the upper limit of median OS reported in other series which ranged from 31–52 months. The median PFS was

26 months and is longer than 7–20 months reported in other series. However, our study showed the same pattern of continuous relapse/or progress and the similar failure of the survival curve to plateau as in studies with Caucasian patients [13–20].

Similarity and Difference to Low-Grade Lymphoma

In low-grade lymphoma, it has been shown that most patients have advanced stage disease (over half have stage IV disease), and CR can be attained with regimens without anthracycline. However, the disease runs an indolently relapsing course and long-term survival is rare. In the case of MCL, the morphology, the high incidence of advanced stage disease, and the attainment of CR without anthracycline, the continuously relapsing or progressing clinical course, and the consequent difficulty of a cure are all consistent with features of a low-grade lymphoma. However, the short median overall and progression-free survival suggest it is not an indolent disease. For instance, the median overall survival for low-grade lymphoma is about 8–10 years [29], but the median OS in our patients (52 months) and other studies (31 month–52 month) with MCL is much shorter.

Comparison With Diffuse Large Cell Lymphoma

In our patients, when OS of MCL is compared with that of DLC lymphoma, the MCL survival curve crosses the DLC lymphoma curve with a similar median overall survival (52 months and 53 months, respectively). Crossing of the survival curves is uniformly observed in all studies where OS of MCL is compared with DLC or intermediate-grade NHL patients [14–16,19]. This pattern shows that the early survival (before the curves crosses) in MCL patients is better than that of DLC patients and thus more closely resembles low-grade lymphoma. However, long-term survival is much worse than that of DLC or intermediate-grade NHL patients. This is possibly due to the transformation to the blastoid variant [13], which is associated with a more aggressive clinical course and prognosis [17,21]. Moreover, the failure of the survival curve to plateau in our study and others' [14–20] reveals the incurable nature of the disease with present treatment strategy in contrast to intermediate-grade lymphoma in which 30–50% of patients can be cured with conventional chemotherapy.

PCR Amplication of *bcl*-1 Rearrangement

Translocation (11;14)(q13;q32) is a recurrent chromosomal aberration in MCL. The translocation results in the juxtaposition of the *bcl*-1 gene downstream to the enhancer sequence of the IG heavy chain gene. This results in the up-regulation of the gene and over-expression of the cyclin D1 protein, which drives cells through the G_1S checkpoint in the cell cycle. Previous studies [6,7] showed that breakpoints at region 11q13 dispersed over more than 100 Kb of genomic DNA. Using three separate probes, rearrangement of the *bcl-1/PRAD* locus was detected in 50–80% MCL cases by Southern blot technique, with about half of these breakpoints involving the major translocation cluster (MTC) locus located approximately 110 Kb centromeric to the *bcl*-1 gene [30]. DNA sequencing confirmed the tight clustering of breakpoints in the *bcl*-1 MTC locus, rendering the rearrangement amenable to PCR amplication which detects most of the MTC/J_H translocations [7,8]. For instance, Rimokh et al. [8] showed that 15 of 16 t(11;14) breakpoints that occurred at the MTC were detected by PCR. In our study, using similar primer at the MTC region and a consensus J_H primer, five of the 12 patients (42%) studied revealed *bcl*-1 rearrangement. This is consistent with other studies that showed 33–39% of patients had rearrangement involving the MTC region by PCR [7,8,24,31]. The median OS of the PCR positive and negative cases were 45% and 63%, respectively ($P = 0.97$). Although the numbers were small, it might suggest that breakpoints in the MTC region might not confer any prognostic significance. This has to be confirmed in a larger study.

The beneficial role of autologous stem cell transplant (ASCT) in MCL has been reported in some studies [32,33] but not in others [34,35] and the exact role of ASCT can only be confirmed by studies with a larger number of patients and longer follow-up. Moreover, the elderly majority of patients and the high incidence of bone marrow involvement in MCL may limit the success and feasibility of this approach.

In conclusion, MCL in Chinese have similar clinical features and treatment outcome as the Caucasian patients. Our study also confirmed that MCL combined the aggressive nature of intermediate-grade lymphoma and the indolently relapsing and thus the incurable nature of low-grade lymphoma. Newer modality of treatment is required.

ACKNOWLEDGMENTS

We the clinical and laboratory staff involved especially Professors Sir David Todd and TK Chan for their advice and inspiration and Miss Vicky Tin for her technical help.

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